REMARKS

Applicants have received and reviewed a final Office Action dated June 3, 2003. Applicants request entry of this amendment and response and reconsideration of the rejection of the claims.

Applicants have canceled claims 12-18, and 34-46 without prejudice or disclaimer. Applicants reserve the right to file a continuation application including the subject matter of the canceled claims.

Applicants have also amended claim 47 to clarify the claimed subject matter. Applicants submit that the amendment to claim 47 is supported throughout the specification including page 22, line 15 to page 23, line 12; Figure 4 and page 97, line 14 to page 98, line 7.

Applicants have added new claims 48 to 63. Applicants submit the newly presented claims are supported throughout the specification including at page 11, line 3; page 13, line 27; page 13, lines 3-27; and page 22, line 15 to page 23, line 12; and page 97, line 10 to page 98, line 4.

35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 12-14, 16-18, 34-38 and 39-47 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Without acquiescing to the rejection and solely to expedite prosecution, Applicants have canceled claims 12-14, 16-18, 34-38 and 39-46, rendering the rejection of these claims moot. Applicants respectfully traverse the rejection with respect to claim 47. Applicants will discuss the rejection insofar as it might apply to the newly presented claims.

Claims 47-53 are directed to a bispecific antibody comprising a first polypeptide with a first or second light chain variable domain, wherein the first and second light chain

[illegible] positions outside of the CDR residues [illegible] antibody

antibody comprising a first and second polypeptide, the first polypeptide which comprises a first heavy chain variable domain, a first multimerization domain, and a [illegible] the second polypeptide comprises a second [illegible]

variable domain, a second multimerization domain and said light chain variable domain. The first and second polypeptides dimerize by interaction of the first and second multimerization domain to form a bispecific antibody. Claims 59 to 63 are directed to a bispecific antibody with a common light chain variable domain that has at least 98% sequence identity to each of the original light chain variable domains of a first and second antibody.

Applicants contend that one of skill in the art reading the specification would be able to prepare the claimed bispecific antibodies without undue experimentation. There are many factors to be considered in an analysis of enablement, including the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation. MPEP 2164.01(a) citing in re Wands, 858 F 2d. 731,737 (Fed. Cir. 1988). Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims.

Applicants submit that one of skill in the art would be able to make and use the claimed bispecific antibodies because Applicants have provided a detailed description of making bispecific antibodies with variable light chain domains having at least 98% or even 100% sequence identity. Applicants have provided several detailed working examples identifying light chains having at least 98% sequence identity for antibodies directed against different antigens. Table 6, Figure 4, and Figure 8 provide pair wise sequence alignments for the light chain variable domains of antibodies with different antigenic specificities. Table 6 shows a pair wise comparison of the sequences of light chain variable domains between antibodies with different antigenic specificities and shows several light chains that have at least 98% sequence identity when the light chain variable domain sequences of two antibodies of different specificities are compared. The

combinations of two different antigenic specificities. This high frequency indicates that a light chain that has at least 98% sequence identity to one another or to the original light

Moreover, Applicants have provided direction to one of skill in the art to align the light chain variable domain sequences and then identify those amino acids residues that differ and could be altered. The Examiner's attention is directed to Example 4 and Figure 4, where Applicants have described the alignment of antibody variable light chain sequences and identify amino acid positions that differ and could be altered yet still retain antigen binding activity. These antibody variable light chains have about 98% sequence identity. The specification further indicates that when the two variable light chains differ in sequence those differences should be outside of the CDR region. (See page 97, line 10 to page 98, line 4) In addition, in Figure 8, Applicants have described several antibody light chain variable domain sequences that have at least 98% sequence identity when clones of anti-Her2 and anti-Ob-r antibody sequences are compared. Thus, contrary to the Examiner's contention, the specification includes other examples of screening for light chains that are not just identical.

Applicants submit that they have described the methods and provided working examples of aligning the sequences and identifying amino acid residues that could be modified. A considerable amount of experimentation can be required as along as the experimentation is routine.

The Examiner also contends that the art of antibody engineering is highly unpredictable. Applicants submit that the Examiner has provided no basis for this statement. Applicants submit the level of skill and knowledge in the art regarding antibody structure is well developed. In addition, several molecular modeling programs can be used to predict and identify which amino acid positions can be varied in antibody structure. Thus, Applicants submit that the knowledge of antibody structure and function is well developed and antibody variable domains can be significantly modified and still maintain structure and function.

Appendix Table 6, Figure 4, and Figure 8. Applicants have also described a method for identifying light chain sequences that have at least 98 % sequence identity between

page 98, line 7). Applicants further disclose that in some embodiments, the light chains were aligned and the amino acid residues that differ between the sequences were identified and could be altered (page 97, lines 27-30). Furthermore, Applicants have disclosed a method of testing the binding specificity of the antibodies of the invention (page 101, line 19 to page 102, lines 15). It would be routine experimentation for one of skill in the art using the methods as described in the invention to determine if the bispecific antibody with a first or second light chain having at least 98% sequence identity would bind to both of the antigens. Some experimentation, even considerable experimentation is permissible if it is routine. Therefore, Applicants respectfully submit that the present disclosure provides substantial guidance in ascertaining species in the claimed genus, for at least these reasons.

Thus, Applicants request withdrawal of the 35 U.S.C. § 112, first paragraph, rejection.

Written Description

The Examiner also rejected claims 12-14, 16-18, 31, 33-45 and 47 under 35 U.S.C. § 112, first paragraph on the grounds that Applicants were not in possession of the claimed invention at the time of filing, because the disclosure fails to adequately describe the claimed genus of compounds. Without acquiescing to the rejection and solely to expedite prosecution, Applicants have canceled claims 12-14, 16-18, 31, and 33-45, rendering the rejection of these claims moot. Applicants respectfully traverse this rejection with respect to claim 47, and will discuss the rejection insofar as it might apply to the newly presented claims.

Applicants remind the Examiner that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as

specification meets the written description requirement depends upon several factors, including:

b) physical and/or chemical properties;

c) functional characteristics;

d) known or disclosed correlation between structure and function;

e) method of making.

Applicants respectfully submit that when the above factors are carefully weighed, the specification describes the claimed subject matter in such a way as to reasonably convey to one of skill in the art that Applicants had possession of the claimed invention.

The Examiner stated that the arguments presented by Applicants fail to show where the specification describes any examples where the light chains are not identical. The Examiner also contends that there does not appear to be support in the specification for first and second light chains having 98 or 99% identity or have 80% identity and have at least one CDR region that has the same sequence.

As an initial matter, Applicants submit that claims 44, 45 and 47 have not introduced new matter. With respect to 98 to 99% sequence identity of the first and second light chain variable domain, the Examiner's attention is directed to page 97, line 10 to page 98, lines 4-7 and Figure 4. With respect to a first and second variable light chain domains having 98% sequence identity and differ only at positions outside of the CDR residues, the Examiner's attention is directed to page 23, lines-9, and page 97, line 24 to page 98, line 7.

Contrary to the Examiner's contention, Applicants have described identification and alignment of light chains that were not identical. Applicants submit that the application describes the genus in a manner that clearly demonstrates Applicants were in possession of the claimed invention. Applicants have disclosed the panning of a large human scFv antibody library for antibodies specific for eleven different antigens (page 96, lines 1-13). After comparing the V_L sequences of the antibodies, Applicants

and Figure 8). Based upon these results, it is likely that light chains that have at least 98% sequence identity can be found for any V_L comparison. In fact, the majority of

Applicants have not only described multiple scFv pairs within the claimed genus, but have produced evidence that Applicants' methods are applicable to identifying a light chain having 98% sequence identity of an antibody for any number of different antigens.

Applicants have also provided in Example 4 structural and functional characteristics of these scFv pairs. Applicants have shown the sequence alignments of some of the antibodies and have identified which amino acid positions differ as well as the location of the CDR regions. Applicants have characterized the bispecific antibodies by electrophoretic mobility shift in apparent molecular weight, by their sequence, and by their binding specificity utilizing standard ELISA procedures.

Therefore, Applicants submit that the specification describes physical and/or chemical properties, structural and functional characteristics, and methods of making or isolating the antibodies of the invention. When all of these factors are weighed, Applicants respectfully submit that one of skill in the art would recognize that Applicants had possession of the claimed invention. Based on the above, Applicants request withdrawal of the rejection.

35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 14 under 35 U.S.C. § 112, second paragraph. The Examiner indicated that the phrase "the original nucleic acid" lacks antecedent basis in claim 13. Applicants have canceled claim 14 , rendering the rejection of this claim moot. Applicants respectfully request withdrawal of the rejection of the claim.

35 U.S.C. § 103

The Examiner rejected claims 12-14, 16-18 and 34-47 as unpatentable over Vaughan (Nature Biotechnology 14:309) in view of Bosslett (U.S. Patent No. 5,591,828)

ordinary skill in the art to engineer a bispecific antibody as described in Bosslett using the common light chains as described in Vaughan in combination with the

the rejection and solely to expedite prosecution, Applicants have canceled claims 12-14, 16-18 and 34-46 rendering the rejection of these claims moot. Applicants respectfully traverse the rejection with respect to claim 47 and discuss the rejection insofar as it might apply to the newly presented claims.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) a suggestion or motivation to, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; and 3) a reasonable expectation of success. Applicants submit that all of these requirements have not been met.

Applicants claims are directed to bispecific antibodies having light chains that have at least 98% sequence identity or have at least 98% sequence identity to each light chain variable domain of a first and second antibody. Production of conventional bispecific antibodies is inefficient due to unwanted pairings of the component heavy and light chains. Co-expression of two different antibodies may produce up to 10 heavy and light chain pairings which results in problematic purification and low yield of bispecific antibodies. Applicants' claims are directed to bispecific antibodies that are easier to purify and have increased yield. By using a light chain that has 98% sequence identity of even 100% sequence identity in the bispecific antibody, the number of different unproductive pairings is reduced. Applicants have shown that in the majority of cases identical or light chains having at least 98% sequence identity can be identified in pairwise combinations of antibodies with two different specificities. This frequency of identical light chains or light chains having at least 98% sequence identity shows that it is feasible to more efficiently produce bispecific antibodies.

1) The references when combined do not teach or suggest all of the

naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities.

selected over other light chains or that these light chains can or should be used in bispecific antibodies. Moreover, this references does not teach or suggest a first and second variable light chain domain that have 98% sequence identity in the regions outside of the CDRs or a common light chain domain that has at least 98% sequence identity to each of the variable light chain domains of a first and second antibody.

The deficiency of the Vaughan et al. reference is not remedied by reference to Bosslet et al. The Bosslet et al. reference is directed to bispecific and oligospecific mono and oligovalent receptors. This reference describes the fusion of F(ab) fragments of antibodies of different specificities by a peptide linker. The Bosslet et al. reference also does not teach or suggest formation of bispecific and oligospecific receptors having a first and second variable light chain that have 98% sequence identity in regions outside of the CDR regions. In addition, the Bosslet et al. references does not discuss or suggest the use of multimerization region in a polypeptide to form a bispecific or oligospecific receptor.

The Carter et al. reference (WO 96/27011) and the Ridgeway et al. reference are directed to forming heteromultimers with a multimerization region. These references do not teach or suggest a heteromultimer with a first and second light chain variable domain that have at least 98% sequence identity. The Ridgeway reference is directed to an antibody/ immunoadhesin bispecific molecule and a first and second light chain are not found in this type of bispecific molecule. The Carter et al reference is directed to forming a multimerization domain and is silent regarding a first and second light chain that have at least 98% sequence identity in the region outside of the CDRs.

Thus, Applicants submit even when all of the cited references are combined they do not teach or suggest all of the elements of the claimed invention. This combination of references does not teach or suggest a bispecific antibody comprising a first and second

identity to each of the light chain variable domains of a first and second antibody. At least for this reason, Applicants submit that the Examiner has not established a prima

2) The Examiner has not established a motivation to combine these references.

The Examiner has not established a motivation to combine these references, but states that the prior art as a whole suggests and teaches the claimed invention. The case law makes clear that in order to avoid hindsight-based obviousness, a teaching or motivation to combine the prior art references must be shown. In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1998). In fact, ". . . particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." Ecolochem Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375 (Fed. Cir. 2000) (emphasis added). "Obvious to try" is not the standard. Ecolochem at 1374. Applicants submit that the examiner has not clearly established a motive to combine or modify the references and that none of the cited references provide a motivation to combine or modify the references.

The Vaughn et al. reference is directed to preparing a scFv phage library of naïve antibody variable domains. The reference describes the construction of large repertoire of single chain Fvs derived from functional V genes. This reference describes that the same light chain is sometimes paired with different heavy chains. This reference does not discuss bispecific antibodies nor does it suggest that identical light chains would occur at a frequency so that they could be selected for use in a bispecific antibody. The reference also does not suggest a bispecific antibody in which the first and second variable light chain domain have at least 98% sequence identity outside the CDR regions or a common light chain variable domain that has at least 98% sequence identity to each of the light chain variable domains of a first and second antibody.

Applicants submit that the Vaughan et al. reference does not provide any

naïve ScFv library. The Vaughan et al. reference does not discuss bispecific antibodies or any problems concerning production and yield of bispecific antibodies. Moreover,

98% sequence identity are found at a frequency so that such light chains can readily be identified for any combination of antigens.

Bosslet et al. reference is directed to forming oligomeric molecules by covalently linking together variable domains using peptide linkers. This reference does not teach or suggest a first and second variable domain that have at least 98% sequence identity in regions outside of the CDRs or common light chain variable domains. Thus, the Bosslet et al. reference also does not provide motivation or suggestion to modify or combine the cited references.

As discussed previously, the Ridgeway et al. reference does not teach or suggest the use of a first and second light chain variable domain as it is directed to an immunoadhesins, and thus does not address the problem of the presence of multiple light chains. The Carter et al. reference is silent regarding the light chains and does not teach or suggest a first and second variable light chain that have at least 98% sequence identity in a region outside of the CDRs or common light chains.

Thus, none of the cited references provide motivation to combine or modify the teaching of the references to achieve Applicants' claimed invention.

Applicants respectfully submit the Examiner is improperly using hindsight reconstruction. As the Federal Circuit stated in In re Fine "we cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention." (In re Fine 837 F2d 1071, 1075 (Fed. Circ. 1998)). As in the In re Fine case, the examiner is picking and choosing isolated disclosures and has not established a suggestion, teaching or motivation to combine these references.

3) The Examiner has failed to show that there would be a reasonable expectation of success in obtaining a bispecific antibody having a first and second variable light chain with at least 98% sequence identity in the region outside of the CDRs.

To establish a reasonable expectation of success, the suggestion of the claimed invention and a reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. In re Vaeck, 20 USPQ2d 1438, 1142 (Fed. Cir. 1991).

Applicants submit that the Examiner has not established a reasonable expectation of success of increasing yields and efficiency of producing bispecific antibodies. None of the cited references teach or suggest a bispecific antibody having a first and second variable light chain having at least 98% sequence identity in region outside of CDR sequences or with a light chain having at least 98% sequence identity to each of variable light chain domain of a first and second antibody or suggest that such a bispecific antibody could be prepared in high yield.

As discussed previously, Vaughan et al. is not directed to the problem of preparing bispecific antibodies much less preparing bispecific antibodies in high yield. There is no teaching or suggestion in Vaughan et al. that bispecific antibodies with light chains that have at least 98% sequence identity can or should be formed. In fact, in Vaughan et al., lack of diversity of the library was viewed as a negative aspect of the library. In addition, Vaughan et al. did not teach or suggest that ScFv with light chains having at least 98% sequence identity would be found in the majority of possible pairwise combinations of two different antigen specificities. The other cited references also do not provide a reasonable expectation of success because none of the cited references suggest a bispecific antibody having light chains with at least 98% sequence identity or that such light chains could be identified at a high enough frequency for any pairwise combination of antibodies having different specificities.

Thus, based on the teachings of these references one of skill in the art would not have had a reasonable expectation of success of preparing a bispecific antibody comprising a first and second light chain having at least 98% sequence identity in a region outside of the CDRs.

Based on the foregoing, Applicants contend the Examiner has not established a prima facie case of obviousness and request withdrawal of the 35 U.S.C. § 103 rejection.

Interview

Applicants request an interview with the Examiner and his supervisor after receipt of these papers. The Examiner is requested to contact Applicants' representative to

Summary

Applicants submit that all pending claims are in condition for allowance, and notice to that effect is earnestly requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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